Docket No.: 20052/1200518-US5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Randolph J. Noelle et al.

Application No.: 09/164,568 | Confirmation No.: 6823

Filed: October 1, 1998 | Art Unit: 1644

For METHODS FOR INDUCING ANTIGEN-SPECIFIC T CELL TOLERANCE | Examiner: P. Gambel

PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Concurrent with the filing of a Notice of Appeal, and in accordance with the Pre-Appeal Brief Conference Program, Applicants hereby request a pre-Appeal Brief review of the final rejection mailed June 14, 2006 in the above-identified application. No amendments are being filed with this request. With all claims having been twice rejected, an appeal is proper in accordance with 37 C.F.R. § 41.31(a).

Claims 82-94 are pending in this application. The sole question on appeal is whether the Examiner is correct in rejecting the claims under 35 U.S.C. § 103 as obvious over Lederman *et al.*, U.S. Patent No. 6,403,091 ("Lederman"), in view of Beschorner *et al.*, U.S. Patent No. 5,597,563 ("Beschorner"), Cobbold *et al.*, U.S. Patent No. 5,690,933 ("Cobbold"), and Eynon *et al.*, *J. Exp. Med.* 175: 131-138, 1992 ("Eynon").

Review is being requested because there is no teaching or suggestion of all of the claim limitations in the references cited by the Examiner, either taken alone or in combination, or a suggestion or motivation to combine the above cited references as done by the Examiner.

The present invention provides a method for reducing antigen-specific T cell responsiveness *in vivo* comprising the administration of (a) an antigen-presenting cell (APC) that presents an autoantigen to an activated T cell expressing mouse or human gp39 **and** (b) an anti-gp39 antibody that binds to mouse or human gp39 on the activated T cell, wherein the anti-gp39 antibody is administered prior to, concurrent

with, or subsequent to administration of the APC in an amount effective to reduce T cell responsiveness to the APC. Thus, the claimed inventive method provides an effective means of inducing T cell tolerance to a soluble antigen or an allogeneic cell.

The Rejection Under 35 U.S.C. § 103 should be withdrawn

The Examiner's position is that Lederman discloses the use of anti-gp39 antibodies to inhibit the immune response in order to treat various autoimmune diseases. The Examiner therefore attempts to cure Lederman's defect with the teachings of Beschorner, Cobbold, and Eynon arguing that they provide the missing limitation of APCs to induce tolerance, and would have been combined with Lederman by one of ordinary skill in the art at the time of the invention with a reasonable expectation of success in arriving at Applicants' claimed invention. (*see* Office Action dated June 14, 2006, page 5). Applicants respectfully disagree.

Applicants submit that the Examiner has failed to present a case of *prima facie* obviousness based on the cited references (*see* Response dated August 9, 2006, pages 3-7). Three basic criteria must be met to establish a *prima facie* case of obviousness: (1) the references taken alone or in combination must teach or suggest all the claimed limitations; (2) suggestion/motivation in the references or in the general knowledge of one having ordinary skill in the art to modify or combine reference teachings; and (3) a reasonable expectation of success (MPEP § 2143).

(1) All the claimed limitations are not taught or suggested by the references taken alone or in combination

As indicated above, the claimed method for reducing antigen-specific T cell responsiveness *in vivo* requires two steps. Both of these steps together as taught by Applicants in claim 82 are not disclosed or suggested by any of the cited references, either alone, or in combination.

With regard to the claim limitation of step (a), Lederman, Beschorner, Cobbold, and Eynon do not teach or suggest the use of an APC that presents an autoantigen to an activated T cell expressing mouse or human gp39. The Examiner acknowledges that Lederman fails to teach co-administration of anti-gp39 antibodies with APCs (*see* Office Action dated October 22, 2002, page 3). Lederman does not provide any functional data using activated T cells, and is completely silent as to the administration of APCs together with the anti-gp39 antibodies (*see* Response dated August 9, 2006, page 5). Beschorner does not suggest or describe administration of APCs with activated T cells as called for in the present claims. Beschorner describes administration of an immunosuppressant having the effect of depleting endogenous APCs in the thymus and thus, the depletion of mature, activated T cells. In other words,

Beschorner discloses administration of APCs in an environment ***devoid*** of activated T cells (*Id.* at page 6). Cobbold is silent as to administering APCs (*Id.* at pages 6-7). Eynon does not suggest or disclose administration of an APC to induce tolerance as in the present claims. Rather, Eynon relies upon administration of an antigen to induce only transient tolerance by contacting small resting T cells and unprimed T cells for presentation to small resting B cells (*Id.* at page 7).

With regard to the claim limitation of step (b), Lederman, Beschorner, Cobbold, and Eynon do not teach or suggest co-administration of the APC from step (a) with an anti-gp39 antibody which binds to mouse or human gp39 on the activated T cell, wherein the anti-gp39 antibody is administered prior to, concurrent with, or subsequent to administration of the antigen-presenting cell in an amount effective to reduce T cell responsiveness to the antigen-presenting cell. As stated above, Lederman does not suggest or disclose co-administration of an anti-gp39 antibody with APCs. Beschorner is silent as to administration of an anti-gp39 antibody with an APC for presentation to an activated T cell. Cobbold fails to disclose or suggest any anti-gp39 antibodies, much less co-administration of APCs with the antibodies. Eynon describes resting T cells, which do not express gp39. Furthermore, Eynon is silent as to administration of anti-gp39 antibodies. (*see* Response dated August 9, 2006, pages 5-7).

Because the limitations of steps (a) and (b) in claim 82 are not taught or suggested by the prior art, either taken alone, or in combination, Lederman, Beschorner, Cobbold, and Eynon do not render Applicants' invention obvious.

(2) There is no suggestion or motivation in the references or in the general knowledge of one having ordinary skill in the art to modify or combine the reference teachings

Applicants respectfully submit that the Examiner over-generalizes the teachings of the cited art, and as a result, overlooks the details of the teachings. He improperly argues that Lederman, Beschorner, Cobbold, and Eynon provide sufficient motivation for one of ordinary skill in the art at the time of the invention to combine the teachings of the foregoing references to arrive at the claimed invention with a reasonable expectation of success, and that such a combination teaches each and every limitation of the claims. As stated above, Lederman does not teach or suggest use of APCs. Furthermore, a skilled worker would recognize that the model system used in Lederman is flawed (*see* Response dated August 9, 2006, pages 4-5). The Examiner attempts to cure Lederman's defect with Beschorner, Cobbold, and Eynon. However, the Examiner's attempts fail: there is no suggestion in the prior art to combine these references because there is no indication in these references as to the success of employing APCs to induce tolerance.

A skilled worker would not have been motivated to combine the teachings of Beschorner with the teachings of Lederman because the skilled worker would recognize that an anti-gp39 antibody can only bind ***activated*** T cells, ***not unactivated*** T cells. Furthermore, a skilled worker also would recognize that contact with an APC is necessary in order for T cells to become "activated" in the thymus and would understand that by administering an immunosuppressant, Beschorner teaches depletion of endogenous APCs in the thymus and thus, the depletion of mature, activated T cells, and any T cell pre-cursors (*see* Response dated August 9, 2006, page 6). Thus, in actuality, Beschorner teaches away from Lederman and one of skill in the art would not have been motivated to combine the teachings of the two references (*Id.*). It is understood that "a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant" (*Tec Air, Inc. v. Denso Mfg. Mich., Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)); *see also In re Lundsford*, 148 U.S.P.Q. 721, 726 (CCPA 1966) (stating that a reference which teaches an opposite concept teaches away, and cannot be properly combined to make an obviousness rejection)).

A skilled worker would not have been motivated to combine the teachings of Cobbold with the teachings of Lederman because the antibody taught by Lederman and the antibody taught by Cobbold each block T and B cell interaction with ***different*** mechanisms. Lederman's antibody blocks the "effector" phase (T cell induced differentiation of B cells into Ig-secreting cells), whereas Cobbold's antibody blocks the "inductive" phase (initial physical interaction of a T cell with a B cell), which is *prior* to the effector phase. Since Cobbold's method is already blocking the "inductive" phase, there would not be an "effector" phase to block following use of Cobbold's anti-CD4 antibody. Thus, one of ordinary skill in the art would not have been motivated to look to Cobbold's teachings in order to block the "effector" phase (*see* Response dated August 9, 2006, page 7).

Finally, a skilled worker would not be motivated to combine the teachings of Eynon with the teachings of Lederman because the skilled worker would recognize that only activated, not resting, T cells express gp39 and Eynon only describes resting T cells. A skilled worker would also recognize that Eynon administers an endogenous APC to test whether T cell tolerance was induced. Thus, Eynon, at best, discloses a method of evaluating whether tolerance occurred, not a method for inducing tolerance. (*Id.*).

Both the motivation to combine the relevant elements and the suggestion of success must be found in the prior art to satisfy the requirements for maintaining an obviousness rejection. *In re The Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("[b]oth the suggestion and the expectation of success

must be founded in the prior art, not in the applicant's disclosure"). While not all elements of the presently claimed method can be found in the cited references, finding various elements piecemeal in separate references is ***not*** sufficient motivation to combine them to arrive at a claimed invention. *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) ("[T]he examiner must show reasons that the skilled artisan, *confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*") (citations omitted, emphasis added). For at least the reasons stated above, a skilled worker would not find a suggestion or motivation to combine any of the cited references to arrive at the claimed invention.

(3) The cited prior art and the knowledge of one of ordinary skill in the art do not give rise to a reasonable expectation of success

Even assuming *arguendo* that the cited references are properly cited and combined, the Examiner has presented a combination of references that provide no reasonable expectation of success for achieving the claimed invention as they do not account for all the claimed limitations that inducing T cell tolerance by administering ***both*** an APC that presents an autoantigen to an activated T cell expressing mouse or human gp39 **and** an anti-gp39 antibody. Thus, one of ordinary skill in the art at the time of the invention would not have been prompted by any combination of the cited prior art and/or their own knowledge to create the claimed method.

Therefore, claim 82 is believed to be patentable over the cited art. In view of the patentability of claim 82, claims 83-94, which depend from this independent claim, are also believed to be patentable. Applicants respectfully request reconsideration and withdrawal of this rejection. For the reasons demonstrated above, the case should be returned to the Examiner with an indication that the application is allowable.

Dated: December 13, 2006

Respectfully submitted,

By _____

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